Development of an Infection-Responsive Fluorescent Sensor for the Early Detection of Urinary Catheter Blockage

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ABSTRACT: Formation of crystalline biofilms following infection by *Proteus mirabilis* can lead to encrustation and blockage of long-term indwelling catheters, with serious clinical consequences. We describe a simple sensor, placed within the catheter drainage bag, to alert of impending blockage via a urinary color change. The pH-responsive sensor is a dual-layered polymeric 'lozenge', able to release the self-quenching dye 5(6)-carboxyfluorescein in response to the alkaline urine generated by the expression of bacterial urease. Sensor performance was evaluated within a laboratory model of the catheterized urinary tract, infected with both urease positive and negative bacterial strains under conditions of established infection, achieving an average 'early warning' of catheter blockage of 14.5 hours. Signaling only occurred following infection with urease positive bacteria. Translation of these sensors into a clinical environment would allow appropriate intervention before the occurrence of catheter blockage, a problem for which there is currently no effective control method.

Catheter-associated urinary tract infection (CAUTI) accounts for approximately 80% of nosocomial infections worldwide [1]. Foley catheters are often used on a long-term (≥30 days) indwelling basis as a common management technique for urinary incontinence or retention, and are universally complicated by polymicrobial and dynamic bacteriuria [2]. Specifically, infections caused by the Gram-negative, motile bacterium *Proteus mirabilis* (*P. mirabilis*) comprise 20-45% of catheter-related infections [1], since *P. mirabilis* readily colonizes all available catheter types to form extensive biofilm communities [3]. Expression of a potent urease enzyme catalyzes the hydrolysis of urea in the urine, resulting in a rapid pH increase. The induced alkaline environment initiates precipitation of polyvalent ions (including struvite ($MgNH_4PO_4{\cdot}6H_2O$) and carbonate-apatite [$Ca_{10}(PO_4CO_3OH)_6(OH)_2$]. Local supersaturation and subsequent accumulation of crystalline biofilms continues within the catheter until the flow of urine is obstructed, resulting in painful distention of the bladder, and serious symptomatic episodes such as acute pyelonephritis and septicemia [4].

Since many long-term catheterized patients are in community care, bacteriological analysis of their urine is rarely performed [5]. Consequently, colonization by *P. mirabilis* often remains undetected until the emergence of severe sequelae. Indeed, there is currently no reliable way of preventing or accurately predicting when blockage may occur. Moreover, patients who commonly suffer from catheter blockage may have regular scheduled catheter changes in their care plan; however the irregularity of encrustation and blockage often results in needless or emergency changes, instigating patient trauma and avoidable healthcare costs [6].

The concept of using urinary pH elevation to provide an 'early warning' of catheter blockage has been explored previously via the covalent linkage of the pH indicator bromothymol blue to cellulose acetate polymer. Despite successful *in vitro* [7] and clinical assessments [8] of this system, this sensor was deemed unsuitable for commercial development. Hence, the system was modified to improve commercial viability via the manufacture of a silicone-based formulation with the incorporated indicator and hydrophilic filler. The sensor was housed within a small polyvinyl chloride connecter, located in the junction between catheter and drainage bag, and proved promising both *in vitro* and in clinical studies. However, the 'early warning' of catheter blockage in human trials was >18 days, thus calling into question whether this system can be considered an indicator of imminent catheter blockage.

Herein, we report the development of a simple 'lozenge' sensor placed directly into the drainage bag, to signal impending catheter encrustation and blockage following infection by *P. mirabilis* utilizing urinary pH as a proxy indicator. The system is based on previously published technology [9], and comprises a cylindrical hydrogel reservoir (poly (vinyl-alcohol) (PVA)), containing the self-quenching fluorescent dye 5(6)-carboxyfluorescein (CF). The hydrogel matrix is completely encapsulated and sealed by a pH-sensitive 'trigger' layer, composed of EUDRAGIT®S 100 (poly(methyl methacrylate-*co*-methacrylic acid)). Elevation of urinary pH following *P. mirabilis* infection causes swelling of the EUDRAGIT®S 100 trigger layer, releasing the dye to result in a clear visual colour change within the catheter drainage bag. Unlike the previously reported technology, the updated system avoids a potential adverse *in vivo* effects such as urethral inflammation [10], or promotion of microbial adhesion via deposition of a conditioning film on the luminal and external catheter surfaces [11]. Furthermore, localized dye release within the drainage bag, without the spatial constraints of the catheter tip allows for a greater concentration of dye to be released within the visible portion of the catheterized urinary tract, resulting in a clear visual colour change of residual urine to warn of impending blockage and allow sufficient time for clinical intervention.

METHODS:

Analysis of 5(6)-Carboxyfluorescein Properties

PH-Dependency

The pH-dependent response of CF was assessed via pH adjustment of 0.5 mM CF solution (in HEPES buffer) within the range of pH 2-10 in 0.5 increments. A SPECTROstar Omega microplate reader (BMG Labtech, UK) was used to monitor fluorescence endpoints, using excitation and emission wavelengths of 485 ± 12 and 520 nm, respectively.

Concentration Quenching

Dilutions from CF stock (50 mM) were undertaken to achieve a concentration range of 10 mM – 10 nM in HEPES buffer. Dilutions were adjusted to pH 6, 7 and 8 accordingly via dropwise addition of NaOH/HCl (1M). Fluorescence endpoint measurements were read on a microplate reader.

Preparation of EUDRAGIT®S 100 Solution

An organic dip coating solution of EUDRAGIT®S 100 (average molecular weight of 150,000 g/mol) (Evonik industries, Germany) was prepared as previously reported [9] and stored at room temperature until required.

Preparation of pH-Sensitive Lozenge Sensors

To CF solution (50 mM, adjusted to pH 6) was added PVA (14,600-18,600 g/mol) (10% w/v) and heated to 97 °C with constant stirring to facilitate diffusion. The resultant hydrogel (1 ml) was cast into a 24-well microplate containing a 2 cm length of sterilized cotton thread, and stored at -20 °C overnight to promote cryogenic gelation. Sensors were thawed at room temperature (4 h) before dip coating with the EUDRAGIT®S 100 trigger layer via suspension from the thread. Sensors were manually dip-coated 50 times, with a 5 minute solvent evaporation period at room temperature between each coating. Coated sensors were stored at 4 °C until required.

Evaluation of Sensor Performance

In Vitro Bladder Models

Bladder model setup and operation was followed as previously reported [9]. Artificial urine was prepared according to [12] and supplied to the bladders via a peristaltic pump at a flow rate of 0.75 ml/min. Models simulating late-stage infection were inoculated directly with clinical isolates of *P. mirabilis* B4 or *E. coli* NMS59 bacteria (10^8 colony forming units/ml (CFU/ml)). Two individual sensors were added aseptically to each drainage bag, and observed visual changes in urine colour were correlated with measured fluorescence response within the drainage bag. Fluorescence emission was quantified using a microplate reader as previously described.

Bacterial Cultures

Prototype sensors were evaluated for species selectivity using live cultures of *P. mirabilis* B4 and *E. coli* NSM59 clinical isolates (~5 x10^6 CFU/ml). To artificial urine media (10 ml) was added bacterial overnight culture (10 µl). Coated sensors were added to subcultures, and changes in pH, and fluorescence response as a function of dye release were measured via sequential sampling.

Results and Discussion

This study describes the initial proof-of-concept development and *in vitro* evaluation of a novel medical device for the advance warning of urinary catheter blockage following infection by *P. mirabilis*. The dual-layered polymeric lozenge sensor is shown in Figure 1.

The sensor provides an *in situ* fluorescent signal, visible to the naked eye, which detects expression of bacterial urease from *P. mirabilis* via the use of pH as a intermediary indicator. The outer 'shell' of the lozenge is formed of the pH-sensitive polymer EUDRAGIT®S 100, containing a ratio of carboxyl: ester groups of 1:2 The pH gradient existing in the drainage bag as a result of the pathological conditions of *P. mirabilis* is sufficient to cause a morphological change in the polymeric structure. Once the pH or the urine media is raised to pH 7, the carboxylic acid moieties become deprotonated, and the network begins to swell as a consequence of repulsion. This allows penetration of the surrounding liquid media, and thus the liberation of the encapsulated fluorescent dye. The resultant colour change within the drainage bag (pale yellow to fluorescent yellow/green) [13].

Diagnosis of CAUTI remains a considerable challenge for clinical staff and point-of-care practitioners. Often, non-evidence based approaches are still considered the most effective at predicting bacteriuria (such as discolored or malodorous urine), with a dipstick of urine being commonly

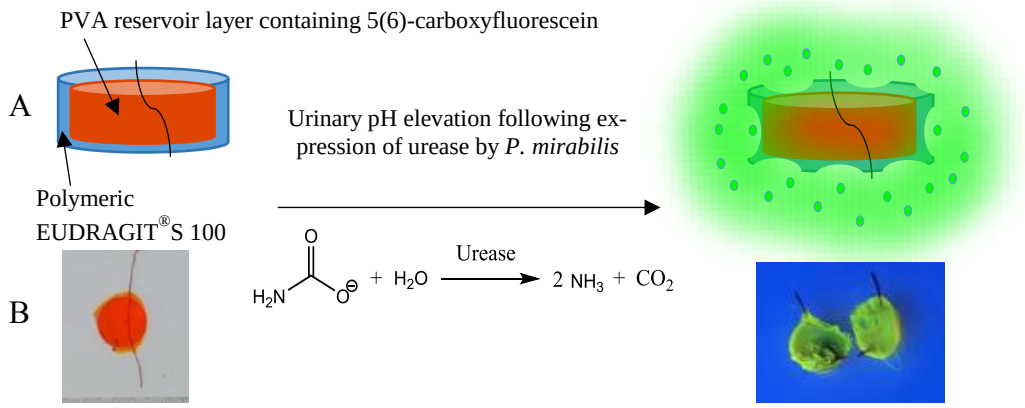

Figure 1. A) Schematic representation and B) photographs of dual-layered polymeric lozenge sensor degradation and release of 5(6)-carboxyfluorescein. Generation of an in situ fluorescent signal provides 'early warning' of catheter blockage via detection of alkaline urine as a result of *P.mirabilis* expression of bacterial urease.

used as a diagnostic tool. As such, catheter-associated asymptomatic bacteriuria (i.e. the presence of bacteria in the urine without clinical symptoms) is often being misdiagnosed as CAUTI and inappropriately treated with antibiotics [14]. The introduction of simple, point-of-care diagnostic devices such as the one described in this report may help to avoid the unnecessary prescription and overuse of antibiotics, thus encouraging a paradigm shift towards targeted prescribing and antibiotic stewardship, potentially aiding the preservation of the utility of antimicrobial agents [15].

Analysis of 5(6)-Carboxyfluorescein

The suitability of CF for the *in situ* sensing of CAUTI, and the mechanism by which the fluorescent signal propagates from the sensors within the drainage bag were important considerations when formulating the prototype sensors.

Recent studies undertaken by Thet *et al.* [16] have investigated the use of CF within a hydrogel wound dressing for the early detection of model pathogenic wound biofilms. Clear colourmetric detection in response to cytotoxins or other virulence factors was achieved, via the release on CF dye from a hydrogel matrix, demonstrating a change in microbiological state and allowing for rapid intervention. This work aims to improve the visual response gained in previous work by releasing CF into a large volume of liquid media, thereby enhancing the colourmetric signal observed.

Above the self-quenching concentration [17] during encapsulation within the hydrogel matrix, the dye is quenched owing to the formation of non-fluorescent dimers. Upon release of the dye into the urine diluent the concentration is sufficiently lowered such that the self-quenching is inhibited and the fluorescence activated (Figure 2A). Furthermore, greater diluent pH has been shown to directly improve the observed fluorescence signal output (Figure 2B). Since the pH of infected urine is highly alkaline (~pH 8), this may further aid the visualization of the resultant urinary color change.

In Vitro Evaluation of Prototype Sensors: Bacterial Cultures

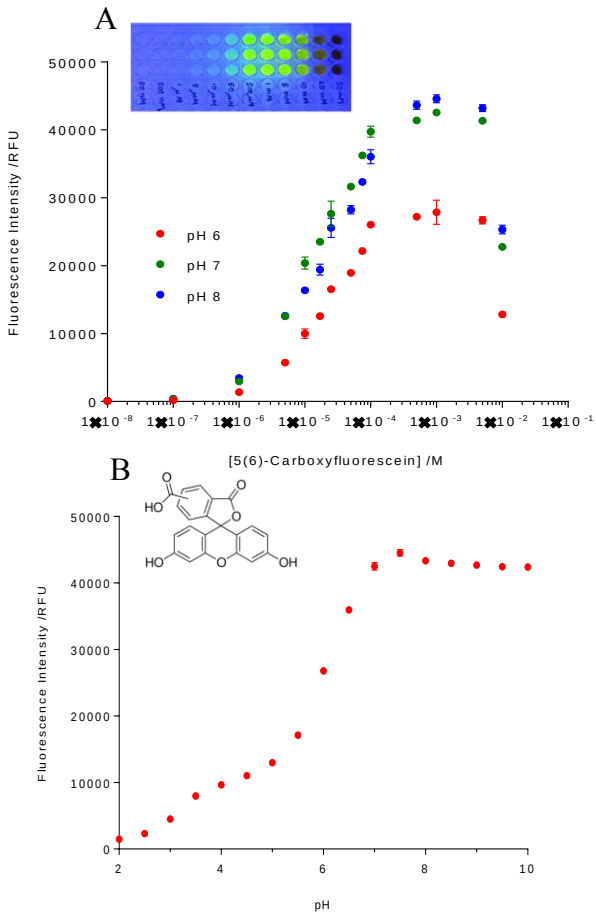

Figure 2. Analysis of 5(6)-carboxyfluorescein properties. A) Dependence of fluorescence emission on CF concentration at pH 6, 7 and 8, showing self-quenching at 10 mM. (Inset: visual representation of CF fluorescence at concentrations 50 nM -50 mM at pH 8). B) Dependence of fluorescence emission on pH. (Inset: chemical structure of CF). Data shown is the mean of triplicate repeats. Error bars represent standard error of the mean (SEM).

Initial assessment of lozenge sensors in artificial urine supernatants of *P. mirabilis* and the urease-negative uropathogen *E. coli* confirmed dye release in response to elevated urinary pH (Figure S1). Further analysis within live

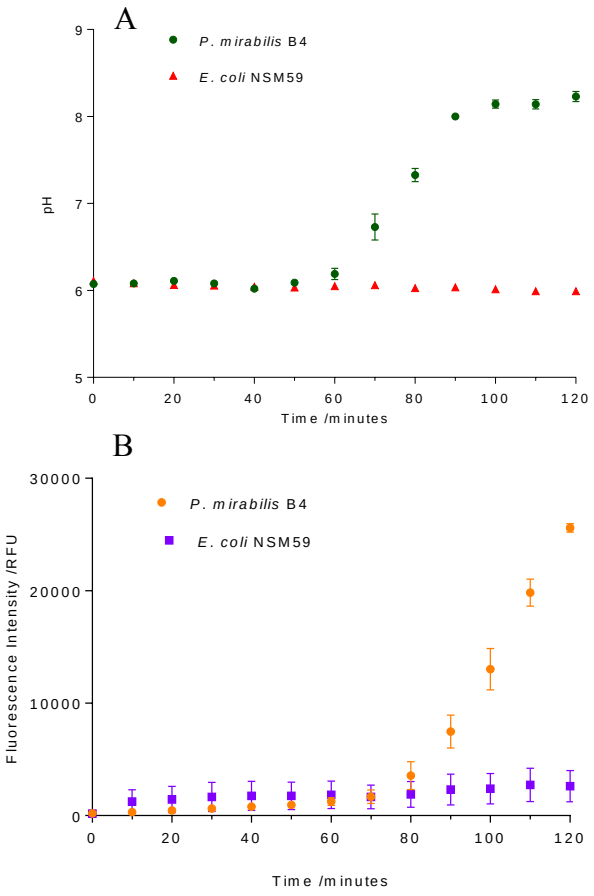

Figure 3. Analysis of sensor performance in 1:100 artificial urine subcultures, modelling the onset of catheter-associated urinary tract infection. A) pH elevation of artificial urine subcultures of *P. mirabilis* B4 and *E. coli* NSM59. B) Corresponding fluorescence emission of prototype sensors upon release of CF dye into artificial urine subcultures. Data shown is the mean of triplicate repeats. Error bars represent SEM.

bacterial cultures exhibited selective release of CF in response to the onset of infection by *P. mirabilis* (Figure 3). Evaluation of sensor performance over a 2 hour period, within which the urinary pH was raised (Figure 3A) from pH 6.1 (corresponding to an infection of 5.3 x10^6 CFU/ml) to 8.55 (corresponding to an infection of 2.3 x10^7 CFU/ml (Figure S2)) was found to correspond to a rapid and observable increase in fluorescence response as a function of CF release from the hydrogel matrix (Figure 3B). No significant fluorescence output was observed within the control culture of *E. coli*, owing to its inability to express urease, and hence, cause catheter blockage.

Investigation into the kinetics of initial CF-release from lozenge sensors (Figure S3) revealed that the rate of release within the first 15 minutes of exposure to buffer at pH 7 was 5.3 x10^{-8} at pH 7 (rising to 1.5 x10^{-7} mol dm^{-3} min^{-1} at pH 8) with a maximum CF release of approximately 3.5 mM after 120 minutes. Hence, despite only approximately 14% of the encapsulated dye being released from the PVA reservoir, the resultant luminescence lies within the most fluorescent concentration region of the fluorescent chromophore (Figure 1A). In effect, the conservation of the majority of the dye within the hydrogel sensor may serve to retain signal strength over a longer period of time.

In Vitro Evaluation of Prototype Sensors: Laboratory Model of Catheterized Bladder

The performance of the dual-layered lozenge sensors to signal the onset of catheter blockage was tested using the *in vitro* bladder model system (originally described by Stickler et al., 1999), which replicates the full closed drainage system, and represents the *in vivo* catheterized urinary tract. Sensor 'switch on' was defined as the point at which a visual colour change was observed in residual urine within the drainage bag. Since the application of this technology requires the signal to be easily observable without the use of specialist equipment, the point of sensor switch on was subjectively judged by eye under ambient lighting. Observation of visual dye release prompted quantitative analysis of urinary fluorescence (Figure 4), such that the concentration of CF in the diluent could be estimated. The response of lozenge sensors to *E. coli* was also assessed to determine the selectivity of the sensors towards urease-positive species.

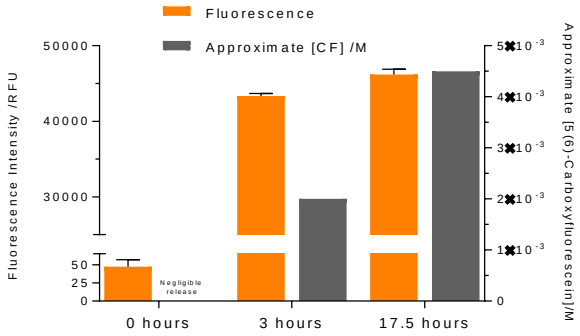

Figure 4: Quantitative analysis of dye release into residual artificial urine of *P. mirabilis*-infected models at experiment start (0 hours), point of visual colour change (3 hours) and catheter blockage (17.5 hours). Data shown are the mean of triplicate repeats. Error bars represent standard error of the mean (SEM).

Dye release and consequent visual urinary colour change within the drainage bags was observed after 3 hours (urine pH 7.2), corresponding to approximately 2 mM CF released (doubling by the point of blockage to ~4 mM) (Figure 4). Average blockage time of *P. mirabilis* infected models occurred at 17.5 hours after the flow of urine to bladders was

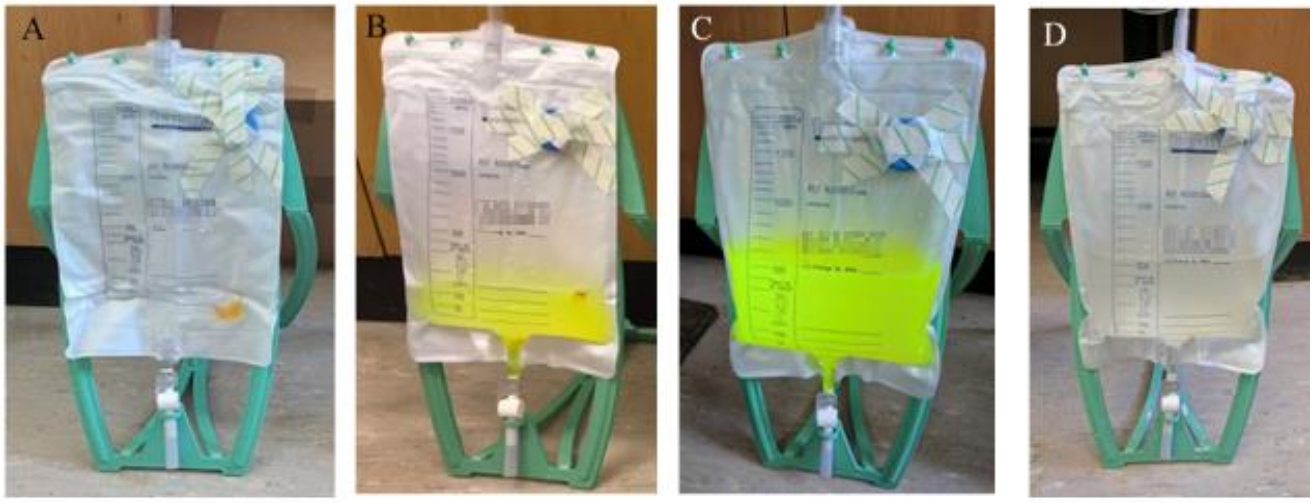

Figure 5. A) Appearance of drainage bag at experiment start (0 hours). B) Point of qualitative visual colour change (3 hours) in bladder model infected with 10^8 CFU/ml *P.mirabilis* B4. C) Colour change of artificial urine at point of catheter blockage (17.5 hours) in bladder model inoculated with *P. mirabilis* B4, and D) in bladder model inoculated with 10^8 CFU/ml *E. coli* NSM59. No visual colour change was observed for the urease-negative species.

initiated (urine pH 8.6). Hence, the bag sensors achieved an average early warning of catheter blockage of 14.5 hours, with a range of 12.5-18 hours. The appearance and progression of a clear and unambiguous colour change (Figures 5A-D) within the drainage bag was comparable with results seen previously [5,9], and was deemed sufficient to allow intervention before the manifestation of serious clinical complications. Control bladders inoculated with *E. coli* exhibited negligible fluorescence emission throughout the duration (23 hours) of the experiment (Figure 5D).

The rapid catheter blockage (17.5 hours) achieved using the *in vitro* model of the catheterized bladder is achieved via inoculation with a large bacterial bioburden (10^8 CFU/ml *P. mirabilis* B4) at the experimental start. This endeavours to replicate conditions within the catheterized urinary tract of patients who frequently undergo recurrent catheter blockage , whereby the blocked catheter is removed and quickly replaced directly into urine cultures of *P. mirabilis* at alkaline pH containing aggregates of microcrystalline material [18].

The problem of blockage recurrence affects up to 50% of patients undergoing long-term indwelling catheterization [19], and sufferers may experience occlusion as soon as 2 days post-catheter reinsertion [20]. Since the sensors tested under these 'worst case scenario' conditions signalled catheter blockage sufficiently early (14.5 hours) to permit clinical intervention, they provide a simple and convenient potential management system for recurring urinary catheter blockage, a problem for which there is no current control method.

The sensor design described in this work provides advantages over work described previously, owing to the specific dissolution pH threshold of the EUDRAGIT®S 100 trigger layer. Since the median healthy urinary pH is 6.2 [21] with a mean range of 5.5-7.0, and the average voided urinary pH of patients with consistently blocking catheters is 7.85 [22], the rapid and reproducible dissolution of EUDRAGIT®S 100 above pH 7 [23] allows for a less ambiguous result and potentially fewer false positives when compared to the previously described bromothymol blue-based sensor [5], which responded to increasing urinary pH over a broad range (pH 6-8).

The design constraints of the current Foley catheter system were also important considerations in the design of the sensor. Since the current catheter design has remained unchanged for decades [24], any technological advances in the control of CAUTI requiring the fabrication of additional components or redesign of the catheter/ closed drainage system may well be rejected by patients and carers alike, owing to the introduction of additional cost or complexity. Indeed, some of these issues were highlighted in the pilot scale clinical trials of the bromothymol blue sensor [6], where the infection indicator was inserted as a connector in the junction between the catheter and drainage bag. Some participants reported leakage around the sensor, or expressed concern over the additional length [6]. In contrast, the work described here fits well with existing manufacturing processes and all available drainage bag designs, although the insertion of the sensor into the bag would need to occur at the point of manufacture, such that the sterility of the closed drainage system is not compromised at the point-of-care. Perhaps the most important advantage of the bag-based system employed here is the potential to incorporate antimicrobial coatings to the catheter tip, for example those containing bacteriophage [25] or metal oxide nanoparticles [26] to create a theranostic system whereby the onset of blockage is delayed by the therapeutic coating (thus extending catheter lifetime), and the subsequent elution/failure of the antimicrobial is signalled by the diagnostic sensor visible within the drainage bag.

Conclusion

In summary, this work describes the development of a simple, drainage bag-based sensor for the early warning of catheter blockage following infection by *P. mirabilis*. Since many patients undergoing long-term indwelling catheterization are in community care, the collection and analysis of urine samples can be problematic. The system described here provides a convenient alternative, allowing the patient or carer to be informed of imminent blockage such that appropriate intervention may be facilitated. Evaluation of coating performance in an *in vitro* bladder model showed that lozenge sensors permitted 14.5 hours warning of catheter blockage under conditions of established infection. However, it is worth noting that this system is not fully representative of the *in vivo* catheterized urinary tract. Further clinical studies are thus required to analyse the coating performance in light of the full complexity and variation of the *in vivo* conditions. Overall, sensor performance was comparable to other reported sensor systems, although the implementation of this approach provides significant advantages both in terms of response location and manufacturing considerations

ASSOCIATED CONTENT

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Supplementary methods; evaluation of sensor performance in artificial urine supernatant; correlation of bacterial bioburden with urinary pH in artificial urine subcultures; kinetics of initial 5(6)-carboxyfluorescein release (PDF).

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest

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REFERENCES

(1) Singha, P.; Locklin, J.; Handa, H. A Review of the Recent Advances in Antimicrobial Coatings for Urinary Catheters. *Acta Biomaterialia* **2017**, *50*, 20–40.

(2) Mobley, H. L. T.; Warren, J. W. Urease-Positive Bacteriuria and Obstruction of Long-Term Urinary Catheters. *Journal of Clinical Microbiology* **1987**, *25*, 2216–2217.

(3) Armbruster, C. E.; Mobley, H. L. T. Merging Mythology and Morphology: The Multifaceted Lifestyle of Proteus Mirabilis. *Nature Reviews Microbiology* **2012**, *10* (11), 743–754.

(4) Norsworthy, A. N.; Pearson, M. M. From Catheter to Kidney Stone: The Uropathogenic Lifestyle of Proteus Mirabilis. *Trends in Microbiology* **2017**, *25* (4), 304–315.

(5) Malic, S.; Waters, M. G. J.; Basil, L.; Stickler, D. J.; Williams, D. W. Development of An 'early Warning' sensor for Encrustation of Urinary Catheters Following Proteus Infection. *Journal of Biomedical Materials Research - Part B Applied Biomaterials* **2012**, *100 B* (1), 133–137.

(6) Long, A.; Edwards, J.; Thompson, R.; Lewis, D. A.; Timoney, A. G. A Clinical Evaluation of a Sensor to Detect Blockage due to Crystalline Biofilm Formation on Indwelling Urinary Catheters. *BJU International* **2014**, *114* (2), 278–285.

(7) Stickler, D. J.; Jones, S. M.; Adusei, G. O.; Waters, M. G. A Sensor to Detect the Early Stages in the Development of Crystalline Proteus Mirabilis Biofilm on Indwelling Bladder Catheters. *Journal of Clinical Microbiology* **2006**, *44* (4), 1540–1542.

(8) Stickler, D. J.; Jones, S. M.; Adusei, G. O.; Waters, M. G.; Cloete, J.; Mathur, S.; Feneley, R. C. L. A Clinical Assessment of the Performance of a Sensor to Detect Crystalline Biofilm Formation on Indwelling Bladder Catheters. *BJU International* **2006**, *98* (6), 1244–1249.

(9) Milo, S.; Thet, N. T.; Liu, D.; Nzakizwanayo, J.; Jones, B. V.; Jenkins, A. T. A. An in-Situ Infection Detection Sensor Coating for Urinary Catheters. *Biosensors and Bioelectronics* **2016**, *81*, 166–172.

(10) Talja, M.; Korpela, A.; Jarvi, K. Comparison of Urethral Reaction to Full Silicone, Hydrogen-Coated and Siliconised Latex Catheters. *BJU International* **1990**, *66* (6), 652–657.

(11) Jacobsen, S. M.; Stickler, D. J.; Mobley, H. L. T.; Shirtliff, M. E. Complicated Catheter-Associated Urinary Tract Infections due to Escherichia Coli and Proteus Mirabilis. *Clinical Microbiology Reviews* **2008**, *21* (1), 26–59.

(12) Stickler, D.; Morris, N.; Winters, C. Simple Physical Model to Study Formation and Physiology of Biofilms on Urethral Catheters. *Methods in Enzymology* **1999**, *310*, 498–501.

(13) Coco, R.; Plapied, L.; Pourcelle, V.; Jerome, C.; Brayden, D.; Schneider, Y.-J.; Preat, V. Drug Delivery to Inflamed Colon by Nanoparticles: Comparison of Different Strategies. *International Journal of Pharmaceutics* **2013**, *440*, 3–12.

(14) Mavin, C.; Mills, G. Using Quality Improvement Methods to Prevent Catheter-Associated UTI. *British Journal of Nursing* **2015**, *24* (18), 22–28.

(15) Peterson, L.; Dalhoff, A. Towards Targeted Prescribing: Will the Cure for Antimicrobial Resistance Be Specific, Directed Therapy through Improved Diagnostic Testing? *Journal of Antimicrobial Chemotherapy* **2004**, *53*, 902–905.

(16) Thet, N. T.; Alves, D. R.; Bean, J. E.; Booth, S.; Nzakizwanayo, J.; Young, A. E. R.; Jones, B. V.; Jenkins, A. T. A. Prototype Development of the Intelligent Hydrogel Wound Dressing and Its Efficacy in the Detection of Model Pathogenic Wound Biofilms. *ACS Applied Materials & Interfaces* **2016**, *8*, 14909–14919.

(17) Chen, R. F.; Knutson, J. R. Mechanism of Fluorescence Concentration Quenching of Carboxyfluorescein in LiposomesL Energy Transfer to Nonfluorescent Dimers. *Analytical Biochemistry* **1988**, *172*, 61–77.

(18) Stickler, D. J.; Feneley, R. C. L. The Encrustation and Blockage of Long-Term Indwelling Bladder Catheters: A Way Forward in Prevention and Control. *Spinal Cord* **2010**, *48* (11), 784–790.

(19) Getliffe, K. The Characteristics and Management of Patients with Recurrent Blockage of Long-Term Urinary Catheters. *Journal of Advanced Nursing* **1994**, *20*, 140–149.

(20) Mathur, S.; Suller, M. T. E.; Stickler, D. J.; Feneley, R. C. L.

Prospective Study of Individuals with Long-Term Urinary Catheters Colonized with Proteus Species. *British Journal of Urology* **2005**, *97*, 121–128.

(21) Rose, C.; Parker, A.; Jefferson, B.; Cartmell, E. The Characterisation of Feces and Urine: A Review of the Literature to Inform Advanced Treatment Technology. *Critical Reviews in Environmental Science and Technology* **2015**, *45* (17), 1827–1879.

(22) Choong, S.; Wood, S.; Fry, C.; Whitfield, H. Catheter Associated Urinary Tract Infection and Encrustation. *International Journal of Antimicrobial Agents2* **2001**, *17* (4), 305–310.

(23) Thakral, S.; Thakral, N. K.; Majumdar, D. K. Eudragit®: A Technology Evaluation. *Expert Opinion on Drug Delivery* **2013**, *10* (1), 131–149.

(24) Feneley, R. C. L.; Hopley, I. B.; Wells, P. N. T. Urinary Catheters: History, Current Status, Adverse Events and Research Agenda. *Journal of medical engineering & technology* **2015**, *39* (8), 459–470.

(25) Milo, S.; Hathaway, H.; Nzakizwanayo, J.; Alves, D. R.; Esteban, P. P.; Jones, B. V.; Jenkins, A. T. A. Prevention of Encrustation and Blockage of Urinary Catheters by Proteus Mirabilis via pH-Triggered Release of Bacteriophage. *Journal of Materials Chemistry B* **2017**, *5*, 5403–5411.

(26) Shalom, Y.; Perelshtein, I.; Perkas, N.; Gedanken, A.; Banin, E. Catheters Coated with Zn-Doped CuO Nanoparticles Delay the Onset of Catheter-Associated Urianry Tract Infections. *Nano Research* **2017**, *10* (2), 520–533.

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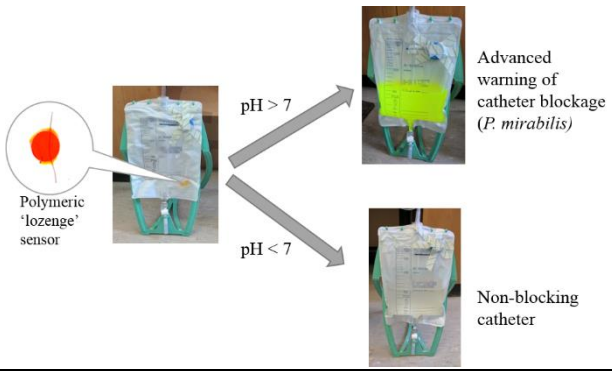
Polymeric
'lozenge'
sensor
pH > 7
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Advanced
warning of
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(*P. mirabilis*)
Non-blocking
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